



## Use of magnesium sulfate before 32 weeks of gestation

### A European population-based cohort study

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# BMJ Open Use of magnesium sulfate before 32 weeks of gestation: a European population-based cohort study

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## ABSTRACT

**Objectives:** The use of magnesium sulfate (MgSO<sub>4</sub>) in European obstetric units is unknown. We aimed to describe reported policies and actual use of MgSO<sub>4</sub> in women delivering before 32 weeks of gestation by indication.

**Methods:** We used data from the European Perinatal Intensive Care in Europe (EPICE) population-based cohort study of births before 32 weeks of gestation in 19 regions in 11 European countries. Data were collected from April 2011 to September 2012 from medical records and questionnaires. The study population comprised 720 women with severe pre-eclampsia, eclampsia or HELLP and 3658 without pre-eclampsia delivering from 24 to 31 weeks of gestation in 119 maternity units with 20 or more very preterm deliveries per year.

**Results:** Among women with severe pre-eclampsia, eclampsia or HELLP, 255 (35.4%) received MgSO<sub>4</sub> before delivery. 41% of units reported use of MgSO<sub>4</sub> whenever possible for pre-eclampsia and administered MgSO<sub>4</sub> more often than units reporting use sometimes. In women without pre-eclampsia, 95 (2.6%) received MgSO<sub>4</sub>. 9 units (7.6%) reported using MgSO<sub>4</sub> for fetal neuroprotection whenever possible. In these units, the median rate of MgSO<sub>4</sub> use for deliveries without severe pre-eclampsia, eclampsia and HELLP was 14.3%. Only 1 unit reported using MgSO<sub>4</sub> as a first-line tocolytic. Among women without pre-eclampsia, MgSO<sub>4</sub> use was not higher in women hospitalised before delivery for preterm labour.

**Conclusions:** Severe pre-eclampsia, eclampsia or HELLP are not treated with MgSO<sub>4</sub> as frequently as evidence-based medicine recommends. MgSO<sub>4</sub> is seldom used for fetal neuroprotection, and is no longer used for tocolysis. To continuously lower morbidity, greater attention to use of MgSO<sub>4</sub> is needed.

## INTRODUCTION

Magnesium sulfate (MgSO<sub>4</sub>) has long been used in obstetric practice. Evidence supports the use of MgSO<sub>4</sub> as a first-line treatment for severe pre-eclampsia and eclampsia.<sup>1</sup> Its previous use as a tocolytic is no longer

## Strengths and limitations of this study

- This is the first study to explore reported policies of use of magnesium sulfate (MgSO<sub>4</sub>) and the actual use in European obstetrical units by indication.
- A major strength of the study is the multinational, prospective population-based sample which includes deliveries in all public and private maternity hospitals in 19 regions in 11 European countries covering over 850 000 births annually securing a high degree of generalisability.
- Another strength is the low risk of interobserver variability between units due to pre-established definitions of diagnoses and terms and pretested questionnaires in all regions.
- Limitations include missing information for validation of severe pre-eclampsia as blood pressures, urine samples and blood chemistry were not collected.

recommended as it was found to be ineffective in inhibiting preterm birth.<sup>2</sup> Currently, it is debated whether MgSO<sub>4</sub> can also be used to protect the immature fetal and neonatal brain. Several meta-analyses found that MgSO<sub>4</sub>, administered prior to preterm birth, decreases risks of cerebral palsy.<sup>3–6</sup> However, some have suggested that additional data are needed before accepting MgSO<sub>4</sub> as an evidence-based therapy for fetal neuroprotection.<sup>7</sup> The biological mechanisms of MgSO<sub>4</sub> are unclear. Possible mechanisms include an ability to decrease the levels of proinflammatory cytokines<sup>8–9</sup> and to dilate fetal cerebral and umbilical arteries.<sup>10–11</sup>

National guidelines concerning administration of MgSO<sub>4</sub> to prevent eclampsia are available in many European countries,<sup>12</sup> and a guideline is also available from the WHO.<sup>13</sup> Only a few countries in Europe, however, including Belgium, Ireland and the UK, have guidelines on the use of MgSO<sub>4</sub> for neuroprotection.<sup>14–16</sup> A Canadian study on the actual use of MgSO<sub>4</sub> was recently published,<sup>17</sup>



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but except for a small, retrospective French single-centre study,<sup>18</sup> data on use of MgSO<sub>4</sub> in Europe are lacking.

We aimed to explore reported policies of use of MgSO<sub>4</sub> and the actual use in European obstetrical units by indication in women giving birth before 32 weeks of gestation using data from a large population-based multiregional cohort.

## MATERIAL AND METHODS

### Study design

This study is based on the analysis of data from the European Perinatal Intensive Care in Europe (EPICE) cohort.<sup>19</sup> This is a population-based, prospective cohort study of infants born at 22+0 weeks to 31+6 weeks of gestation in 19 regions in 11 countries in Europe (Belgium, Denmark, Estonia, France, Germany, Italy, the Netherlands, Poland, Portugal, Sweden and the UK).

Data were collected on all births in each region during varying 12-month periods between April 2011 and September 2012, with the exception of France where the inclusion period lasted 6 months. Clinical data were collected from medical records in 431 obstetric and their associated neonatal units following a standardised protocol, established by a scientific committee and pretested before data collecting began. Data were cross-checked with maternity registers or other external data sources.

In the spring of 2012, a unit questionnaire was also sent by mail or email to department heads of obstetrical and neonatal units caring for infants in the cohort. Units with a neonatal department admitting at least 10 very preterm infants per year were included in this study. The unit questionnaires collected information on the structural characteristics and protocols and policies related to the care of very preterm infants. The questionnaire was pretested outside of the study regions in all countries.

### Data and definitions

We used data from the cohort study on maternal, pregnancy and fetal characteristics including maternal age, gestational age, intrauterine growth restriction (IUGR), sex of the fetus, number of fetuses, parity, in utero transfer, pregnancy complications, use of prenatal corticosteroids (at least one injection), caesarean section (prelabour or after onset of labour), indication for the caesarean section (fetal reasons, maternal reasons or unit policy) and administration of MgSO<sub>4</sub> before delivery (including timing of first dose and total dose). Gestational age was defined as the attending obstetrician's best estimate based on last menstrual period, obstetric history or prenatal ultrasound.

Pregnancy complications were pre-eclampsia, HELLP, eclampsia, antepartum haemorrhage (after 20 weeks), admission to hospital for preterm labour after 20 weeks and infection if this was an indication for delivery. The definition of these conditions was established prior to

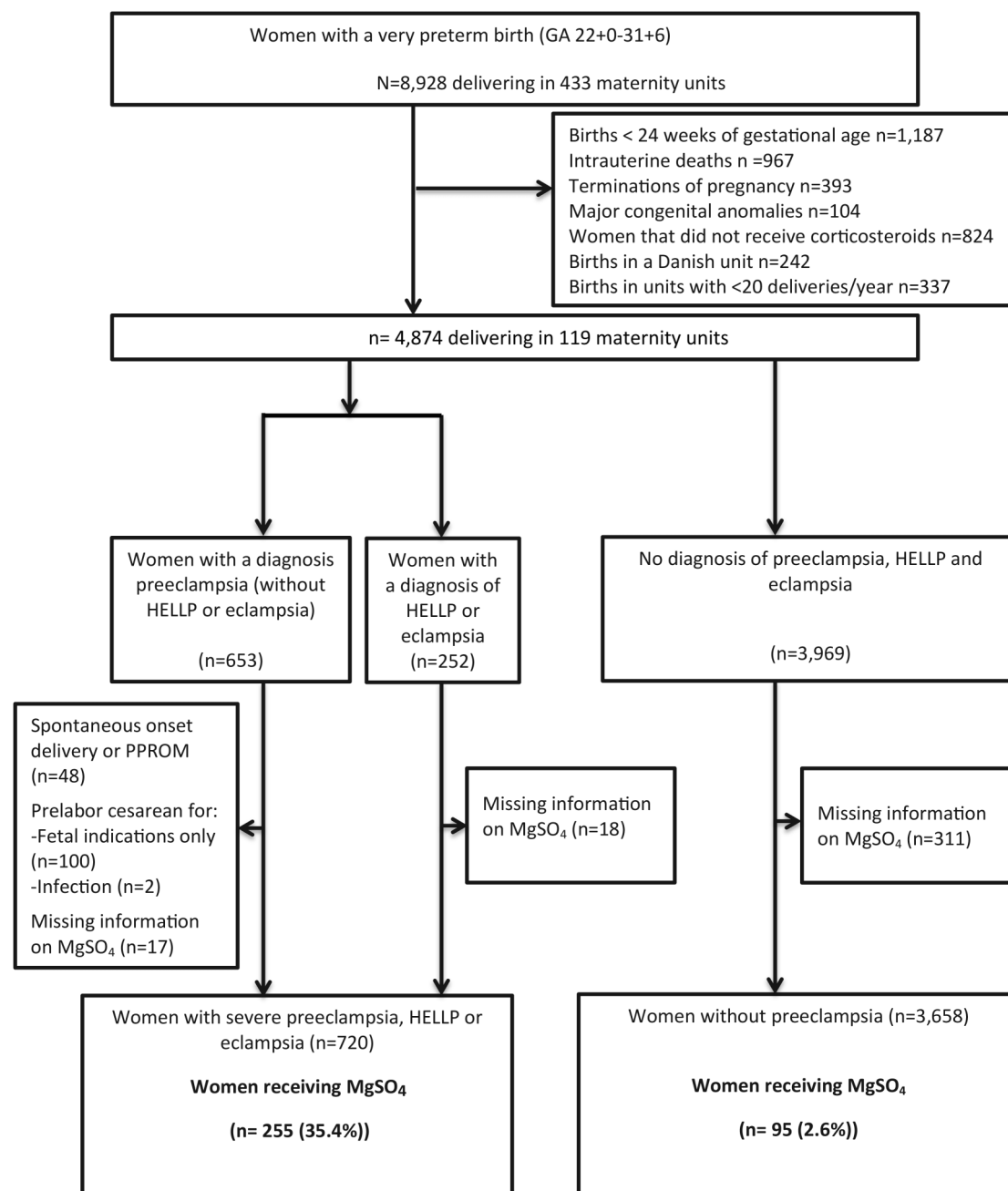
data collection. Pre-eclampsia was a specific item collected in the EPICE study and was defined as proteinuria and systolic blood pressure  $\geq 140$  mm Hg and/or diastolic blood pressure  $\geq 90$  mm Hg occurring after gestational week 20+0 in a woman who was normotensive prior to becoming pregnant. Proteinuria was defined as  $\geq 300$  mg/L protein in a random specimen or an excretion of 300 mg/24 hours. Hypertension had to be confirmed by two separate measurements. HELLP syndrome was defined as a cluster of laboratory abnormalities including serum lactic dehydrogenase  $>600$  U/L, serum aspartate aminotransferase or serum alanine aminotransferase  $>70$  U/L and platelet count  $<100\,000/\text{mm}^3$ . Eclampsia was defined as the onset of seizures in a woman with pre-eclampsia.

From the obstetrical unit questionnaire, we used information on reported treatment policies and practices for treatment of preterm labour and for use of MgSO<sub>4</sub>. The units were asked if "in your unit, magnesium sulfate is used to treat pre-eclampsia or for fetal neuroprotection". Possible responses were 'whenever possible', 'sometimes' or 'never'. Information on the first-line tocolytics used in the unit was also collected.

### Study population

We defined two populations in order to assess use of MgSO<sub>4</sub> for severe pre-eclampsia or for fetal neuroprotection (see [figure 1](#) for the study flow chart). For both populations, we excluded women giving birth before 24 +0 weeks of gestation due to expected differences in levels of treatment for this extremely low gestational age. We also excluded women who had not received prenatal steroids. We hypothesised that if there had been time to administer steroids, MgSO<sub>4</sub> could also have been given. We also excluded all Danish units in the sample as they were participating in a national, randomised, double-blinded controlled trial of the use of MgSO<sub>4</sub> for fetal neuroprotection in preterm birth during the study period. Finally, units with fewer than 20 very preterm deliveries per year were excluded in order to focus on units which regularly cared for high-risk pregnancies and to obtain a sufficient sample size to assess use at the unit level.

The first population included women who had severe pre-eclampsia. We could not use the commonly accepted criteria<sup>20</sup> for severe pre-eclampsia as information on blood pressures, urine samples, blood chemistry and symptoms was not collected. Instead, we defined severe pre-eclampsia as a diagnosis of eclampsia or HELLP, regardless of mode of delivery or as a diagnosis of pre-eclampsia combined with a prelabour caesarean section performed for maternal indications before 32 weeks of gestation. We excluded women who had prelabour caesarean sections for fetal indications (eg, IUGR, fetal distress), due to intrauterine infection or in association with preterm prelabour rupture of membranes (PPROM).



**Figure 1** Flow chart—definition of study populations and use of MgSO<sub>4</sub>. MgSO<sub>4</sub>, magnesium sulfate; PPROM, preterm prelabour rupture of membranes.

The second population was constituted of women without a diagnosis of pre-eclampsia, eclampsia or HELLP; we surmised that in this group, MgSO<sub>4</sub> would be given for indications unrelated to pre-eclampsia, that is, fetal neuroprotection or tocolysis.

### Analysis strategy

We first described the characteristics of the two populations included in our study and then described units' reported policies for use of MgSO<sub>4</sub> as well as the actual use in these units by indication (the per cent of women in each relevant population receiving MgSO<sub>4</sub> in each unit). We then explored maternal, pregnancy and

neonatal factors as well as unit policy associated with MgSO<sub>4</sub> use in the cohort, using univariable and multivariable analyses. For multivariable analyses, we used mixed-effect logistic models to take into consideration the hierarchical structure of our data (correlation between observations within regions).

In sensitivity analyses, we removed all pre-eclamptic pregnancies associated with antenatally detected IUGR to remove situations in which the indicated delivery may have been for fetal reasons. We also compared our final models including patient and unit variables with a model including only patient level factors. Finally, we assessed the impact of excluding units with fewer than

20 very preterm births from our study population by comparing policies in included and excluded units and the women delivering in these units.

Analyses were carried out using STATA version 13.1 SE (Stata Corporation, College Station, Texas, USA).

## RESULTS

In the EPICE cohort, 4874 women from 119 different units were considered for the study after exclusions; the final analysis included 4378 women after further exclusions of cases with pre-eclampsia associated with spontaneous onset of labour, PPRM or cesarean section for fetal reasons, as well missing data on MgSO<sub>4</sub> (see [figure 1](#) for the study flow chart). Of these women, 720 were classified as having severe pre-eclampsia, eclampsia or HELLP; 3658 were classified as not having these conditions. Among women with severe pre-eclampsia, eclampsia or HELLP, 35.4% received MgSO<sub>4</sub> before delivery ([figure 1](#)). This proportion was 33.7% for pre-eclamptic women without either a diagnosis of HELLP or eclampsia (data not shown). Among women without pre-eclampsia, eclampsia or HELLP, only 2.6% received MgSO<sub>4</sub> before delivery.

[Table 1](#) describes the study populations. As expected, the maternal and pregnancy characteristics of the pre-eclamptic and non-pre-eclamptic women differed. Women with severe pre-eclampsia were slightly more likely to have both lower and higher ages and were more often primiparous. They also had lower rates of deliveries at extremely preterm gestations (<26 weeks of gestation). The proportion of female infants was higher in the pre-eclamptic population than in the non-pre-eclamptic population (54.2% and 45.2%, respectively). The proportion of multiple pregnancies was lower in the pre-eclamptic population than in the non-pre-eclamptic population. IUGR was diagnosed before birth in 41.3% of the cases in the pre-eclamptic population, and in 12.8% of the cases in the non-pre-eclamptic population. The number of in utero transfers in the two populations was similar, but the rates of caesarean sections were much higher in the pre-eclamptic population (99.2% and 60.4%, respectively).

[Table 2](#) shows the policies as well as the actual use of MgSO<sub>4</sub> in European obstetrical units. For severe pre-eclampsia, eclampsia or HELLP, most units reported using MgSO<sub>4</sub> whenever possible (41.2%) or sometimes (41.2%). Practices reflected policies. Units reporting use of MgSO<sub>4</sub> whenever possible had higher median rates of MgSO<sub>4</sub> use than units reporting a policy of MgSO<sub>4</sub> use sometimes (25.0% vs 12.5%). However, many units did not use MgSO<sub>4</sub> over the study period (as seen by the IQR) despite a reported policy treatment. Only 5 of 119 units said that they did not use MgSO<sub>4</sub> for severe pre-eclampsia, eclampsia or HELLP and this was consistent with observed rates of use. Ten units did not respond to the question of MgSO<sub>4</sub> treatment for severe pre-eclampsia, eclampsia or HELLP and 6 units did not return the questionnaire; in these 16 units, MgSO<sub>4</sub> was used over the study period.

For fetal neuroprotection, very few units reported using MgSO<sub>4</sub> whenever possible (7.6%); a further 16.0% reported a policy of MgSO<sub>4</sub> treatment sometimes. Observed rates varied by unit responses, but rates were low even in units that had a policy of MgSO<sub>4</sub> treatment 'whenever possible'; the median rate of MgSO<sub>4</sub> treatment of women in the non-pre-eclamptic population was 14.3%.

Only 1 unit (<1%) with a small number of women in the study population reported using MgSO<sub>4</sub> as a first-line tocolytic.

[Table 3](#) provides data on policies and observed use of MgSO<sub>4</sub> when regions are grouped by country. There was a large variability in both unit policies and actual use among women (online supplementary table S1 provides information on the study population and the exclusion criteria as applied to each country). Some countries appeared to use MgSO<sub>4</sub> routinely for severe pre-eclampsia, eclampsia or HELLP, whereas use was much lower in others (France, Italy and Portugal). Use in the non-pre-eclamptic population was low in all study regions, and in 6 of 10 countries, fewer than 3% of women in the non-pre-eclamptic population were treated with MgSO<sub>4</sub>.

[Table 4](#) shows the factors associated with greater use of MgSO<sub>4</sub> in the pre-eclamptic and the non-pre-eclamptic population. For women in the pre-eclamptic population, a gestational age between 26+0–28+6 weeks and/or having a diagnosis of eclampsia was associated with more frequent use of MgSO<sub>4</sub>. In the same population, having a diagnosis of IUGR or HELLP and admission for preterm labour were associated with less frequent use of MgSO<sub>4</sub>. While the proportion of women receiving MgSO<sub>4</sub> was higher in units reporting use whenever possible, the difference was not significant in adjusted analyses. In the non-pre-eclamptic population, gestational ages from 24+0–25+6 to 26+0–28+6 were associated with more frequent use of MgSO<sub>4</sub>, whereas lack of a unit policy on the use of MgSO<sub>4</sub> was associated with less frequent use. In the non-pre-eclamptic group, being hospitalised for preterm labour was not associated with use of MgSO<sub>4</sub>.

Sensitivity analyses showed similar results in the pre-eclamptic group when cases with antenatal detection of IUGR were removed (see online supplementary table S2) and individual patient level characteristics had a similar impact in models without unit policy variables (see online supplementary table S3). Policies and practices in the 10 units in the unit study that were excluded because they had fewer than 20 very preterm births per year were not significantly different from units included in our study (see online supplementary table S4).

## DISCUSSION

### Main findings

This large, population-based observational study yielded three main findings on the use of MgSO<sub>4</sub> for very preterm birth in European obstetric units. First, we



**Table 1** Description of women delivering between 24+0 and 31+6 weeks of gestation with severe pre-eclampsia, eclampsia or HELLP (population 1) and without a diagnosis of pre-eclampsia, HELLP or eclampsia (population 2)

	Women with severe pre-eclampsia* (n=720) n (%)	Women without pre-eclampsia, HELLP or eclampsia (n=3658) n (%)	p Value
Maternal age (years)			
<25	138 (19.3)	631 (17.3)	0.037
25–34	364 (50.8)	2044 (56.0)	
≥35	214 (29.9)	972 (26.7)	
Parity			
Primiparous	474 (66.2)	1944 (53.5)	<0.001
Multiparous	242 (33.8)	1690 (46.5)	
Gestational age (weeks)			
24+0–25+6	48 (6.7)	453 (12.4)	<0.001
26+0–28+6	216 (30.0)	1148 (31.4)	
29+0–31+6	456 (63.3)	2057 (56.2)	
Diagnosis of IUGR			
No	421 (58.7)	3173 (87.2)	<0.001
Yes	296 (41.3)	466 (12.8)	
Sex of baby			
Male	329 (45.8)	2006 (54.8)	<0.001
Female	390 (54.2)	1652 (45.2)	
Type of pregnancy			
Singleton	682 (94.7)	2846 (77.8)	<0.001
Multiple	38 (5.3)	811 (22.2)	
Pregnancy complications			
Eclampsia	51 (7.2)	–	<0.001
HELLP	198 (27.8)	–	
Antepartum haemorrhage	26 (3.7)	865 (23.9)	
Admission for preterm labour	35 (4.9)	1974 (54.4)	<0.001
PPROM	–	1283 (35.2)	<0.001
Infection as indication for delivery	–	421 (12.2)	<0.001
In utero transfer	249 (35.0)	1242 (34.2)	0.668
Mode of delivery			
Vaginal	6 (0.8)	1441 (39.6)	<0.001
Caesarean	709 (99.2)	2195 (60.4)	

\*Defined as a diagnosis of eclampsia or HELLP, regardless of mode of delivery or a diagnosis of pre-eclampsia and a prelabour caesarean section.  
HELLP, Haemolysis, elevated liver enzymes, low platelets; IUGR, intrauterine growth restriction; PPRM, preterm prelabour rupture of membranes.

found that severe pre-eclampsia, eclampsia and HELLP were treated with MgSO<sub>4</sub>, but not as frequently as evidence-based medicine recommends. Second, we found that MgSO<sub>4</sub> was seldom used for fetal neuroprotection, and third, that MgSO<sub>4</sub> is no longer used for tocolysis.

### Strengths and limitations

The strengths of the study are its multinational, prospective population-based sample which includes deliveries in all public and private maternity hospitals in 19 regions in 11 European countries covering over 850 000 births annually. Also, both tertiary and non-tertiary centres were included. This ensures high generalisability to a wide range of settings. The risk of interobserver variability between units was minimised by using pre-established definitions of diagnoses and terms and pre-testing questionnaires in all regions.

Limitations include some missing data on administration of MgSO<sub>4</sub>. We also did not have indications for MgSO<sub>4</sub> use and therefore created subgroups of patients likely to receive MgSO<sub>4</sub> for severe pre-eclampsia or neuroprotection. In the group of women without pre-eclampsia, we assumed that MgSO<sub>4</sub> was given either for neuroprotection or tocolysis. For women with pre-eclampsia, we could not validate the diagnosis of severe pre-eclampsia as blood pressures, urine samples and blood chemistry were not collected, but we assumed that a pre-eclamptic condition resulting in a prelabour caesarean section on maternal indication before 32 weeks of gestation was most likely to be severe. While we excluded prelabour caesareans for fetal indications and intrauterine infection in order to remove women unlikely to have severe pre-eclampsia, some caesareans could have been carried out primarily for IUGR, even if maternal reasons were also indicated. To address this

**Table 2** Policies and observed use of MgSO<sub>4</sub> for severe pre-eclampsia, eclampsia or HELLP, for fetal neuroprotection or for tocolysis in women delivering very preterm (<32 weeks of gestation) in European obstetrical units

	Maternity units (n=119) n (%)	Women with severe pre-eclampsia (n=720) n (%)	Percentage of pre-eclamptic women receiving MgSO <sub>4</sub> in units Median (IQR)	Women without pre-eclampsia, eclampsia or HELLP (n=3658) n (%)	Percentage of non-pre-eclamptic women receiving MgSO <sub>4</sub> in units Median (IQR)
Unit policy for pre-eclampsia					
MgSO <sub>4</sub> whenever possible	49 (41.2)	296 (41.1)	25.0 (0–60.0)	1623 (44.4)	0 (0–3.0)
MgSO <sub>4</sub> sometimes	49 (41.2)	339 (47.1)	12.5 (0–42.9)	1554 (42.5)	0 (0–0)
Never	5 (4.2)	32 (4.4)	0 (0–0)	145 (4.0)	0 (0–0)
No response*	16 (13.4)	53 (7.4)	34.8 (0–60.0)	336 (9.2)	0 (0–1.4)
Unit policy for neuroprotection					
MgSO <sub>4</sub> whenever possible	9 (7.6)	69 (9.6)	33.3 (16.7–72.7)	260 (7.1)	14.3 (0–37.8)
MgSO <sub>4</sub> sometimes	19 (16.0)	118 (16.4)	20.0 (0–60.0)	749 (20.5)	0 (0–4.8)
Never	70 (58.8)	454 (63.1)	11.8 (0–50.0)	2173 (59.4)	0 (0–0)
No response†	21 (17.6)	79 (11.0)	36.4 (0–60.0)	476 (13.0)	0 (0–1.9)
MgSO <sub>4</sub> is a first-line tocolytic	1 (0.88)	0 (0.0)	0.0	8 (0.2)	0.0

\*Includes 10 units that returned the questionnaire, but did not respond to this question and six units that did not return the unit questionnaire.

†Includes 15 units that returned the questionnaire, but did not respond to this question and six units that did not return the unit questionnaire.

MgSO<sub>4</sub>, magnesium sulfate.

issue, we carried out a sensitivity analysis removing these cases and our results were similar.

### Interpretation

Despite global consensus about its effectiveness and safety for preventing eclampsia, only 41.2% of the units reported use of MgSO<sub>4</sub> whenever possible in case of pre-eclampsia and MgSO<sub>4</sub> was used in only 35.4% of women with severe pre-eclampsia, eclampsia or HELLP. This might be a slight underestimation as only antenatal use was registered. A Canadian study from 2015 found a discrepancy between national and local guidelines.<sup>17</sup> In the Canadian study, 79% of women with severe pre-eclampsia received MgSO<sub>4</sub>. However, this estimate was based on only 174 patients and suffered from variation in the definition of severe pre-eclampsia. We found wide country variation in use of MgSO<sub>4</sub>, with lower use in France, Italy and Portugal. While studies on practices of MgSO<sub>4</sub> use in European countries are lacking, several studies have examined MgSO<sub>4</sub> administration for women with eclampsia and have documented low use for prevention in these cases.<sup>21–23</sup>

Our results are also in line with evidence from Mexico and Thailand showing that MgSO<sub>4</sub> is underused in women with pre-eclampsia and eclampsia.<sup>24</sup> Multiple barriers have been identified in low-income and middle-income countries, including failure in registration, distribution, unmet training needs, suboptimal implementation of guidelines and reluctance of staff to use MgSO<sub>4</sub> because of required intensive patient monitoring.<sup>24–27</sup> High-income countries have fewer barriers for accessing antenatal care, early diagnosis of pre-eclampsia and follow-up during and after delivery. However, the same challenges may exist with respect to medical staff concerns about the handling of MgSO<sub>4</sub>

and risks of serious maternal side effects, such as respiratory arrest, arrhythmia and pulmonary oedema.

The evidence that MgSO<sub>4</sub> is an ineffective tocolytic appears to be integrated into clinical practice. Only 1 unit reported using MgSO<sub>4</sub> as a first-line tocolytic and use was not higher among women admitted to hospital for preterm labour in the non-pre-eclamptic population.

Despite the Cochrane meta-analysis published in 2009,<sup>5</sup> an ACOG guideline from March 2010<sup>28</sup> and an RCOG scientific impact statement in August 2011<sup>29</sup> all recommending use of MgSO<sub>4</sub> for fetal neuroprotection, this study reveals an almost non-existing use of MgSO<sub>4</sub> for fetal neuroprotection in Europe in the study period. The reluctance to adopt this practice may be due to the trial sequential analysis from 2011 concluding that randomisation of an additional 400 women was needed to obtain sufficient evidence to introduce MgSO<sub>4</sub> as a standard treatment for neuroprotection.<sup>7</sup> Other possible explanations are the fairly high number-needed-to-treat of 56 (95% CI 26 to 187) to prevent cases of cerebral palsy in deliveries before 34 weeks of gestation,<sup>30</sup> lack of clinical guidelines, and concerns for adverse drug effects necessitating intense monitoring when administering MgSO<sub>4</sub>. Finally, some obstetricians might be waiting for the results of an ongoing randomised controlled trial from Denmark expected in 2018.<sup>31</sup>

Since our study, new guidelines for neuroprotection were issued in two of the countries participating in EPICE, the UK in November 2015<sup>14</sup> and Belgium in July 2014.<sup>16</sup> Guidelines were also issued in Ireland, which is not part of EPICE.<sup>15</sup> In both guidelines, MgSO<sub>4</sub> is highly recommended for neuroprotection to women presenting with imminent preterm birth before 32 weeks of gestation. It is therefore possible that practices have evolved

**Table 3** Policies and observed use of MgSO<sub>4</sub> treatment for very preterm birth (<32 weeks of gestation) by indication and country

Country (region)	Units n	Whenever possible for pre-eclampsia Percentage of units	Women with severe pre-eclampsia n	Women receiving MgSO <sub>4</sub> Per cent	Whenever possible or sometimes for neuroprotection Percentage of units	Women without pre-eclampsia, HELLP or eclampsia n	Women receiving MgSO <sub>4</sub> Per cent
Belgium (Flanders)	9	33.3	70	67.1	11.1	367	2.7
Estonia (whole country)	3	33.3	19	21.1	0.0	93	3.2
France (Northern region, Burgundy, Ile-de-France)	21	0.0	155	18.1	23.8	550	2.0
Germany (Hesse, Saarland)	13	53.9	45	40.0	30.8	228	6.6
Italy (Lazio, Emilia-Romania, Marche)	20	50.0	107	15.9	25.0	620	1.1
Netherlands (East-Central)	2	50.0	45	91.1	50.0	206	0.5
Poland (Wielkopolska)	2	100.0	5	60.0	100.0	114	12.3
Portugal (Northern and Lisbon)	13	76.9	88	9.1	38.5	399	5.5
Sweden (Stockholm)	4	0.0	40	40.0	0.0	147	0.0
UK (Northern, East Midlands, Yorkshire & Humber)	32	46.9	146	50.0	15.6	934	1.3

Women with a non-anomalous live birth who received prenatal corticosteroids and delivered in a maternity unit with more than 20 very preterm deliveries annually (see online supplementary table S1 for exclusions by country).  
MgSO<sub>4</sub>, magnesium sulfate.



**Table 4** Maternal and unit factors associated with MgSO<sub>4</sub> treatment of women with severe pre-eclampsia, eclampsia or HELLP or fetal neuroprotection in women without pre-eclampsia, eclampsia or HELLP

Receiving MgSO <sub>4</sub>	Women with severe pre-eclampsia* (255/720)				Women without pre-eclampsia, HELLP or eclampsia (95/3658)			
	n/N	Per cent	aOR	95% CI	n/N	Per cent	aOR	95% CI
Maternal age (years)								
<25	58/158	42.0	1.32	(0.72 to 2.41)	24/631	3.8	1.68	(0.84 to 3.35)
25–34	131/364	36.0	0.89	(0.56 to 1.42)	47/2044	2.3	0.86	(0.48 to 1.55)
≥35	64/214	29.9	Ref.		24/972	2.5	Ref.	
Parity								
Primiparous	77/242	31.8	1.07	(0.7 to 1.65)	44/1690	2.6	0.84	(0.51 to 1.36)
Multiparous	177/474	37.3	Ref.		50/1944	2.6	Ref.	
Gestational age (weeks)								
24+0–25+6	18/48	37.5	1.71	(0.78 to 3.74)	18/453	4.0	2.31	(1.13 to 4.74)
26+0–28+6	86/216	39.8	1.64	(1.07 to 2.51)	36/1148	3.1	1.71	(1.02 to 2.86)
29+0–31+6	151/456	33.1	Ref.		41/2057	2.0	Ref.	
Diagnosis of IUGR								
No	161/421	38.2	Ref.		79/3173	2.5	Ref.	
Yes	92/296	31.1	0.65	(0.43 to 0.99)	14/466	3.0	1.12	(0.54 to 2.33)
Sex of baby								
Male	112/329	34.0	0.89	(0.6 to 1.32)	54/2006	2.7	0.90	(0.55 to 1.45)
Female	143/390	36.7	Ref.		41/1652	2.5	Ref.	
Type of pregnancy								
Singleton	13/38	34.2	1.19	(0.47 to 3.03)	12/811	1.5	1.80	(0.92 to 3.54)
Multiple	242/682	35.5	Ref.		83/2846	2.9	Ref.	
Pregnancy complications								
Eclampsia	23/51	45.1	2.21	(1.03 to 4.71)	–	–	–	–
HELLP	72/198	36.4	0.60	(0.37 to 0.97)	–	–	–	–
Antepartum haemorrhage	7/26	26.9	0.49	(0.15 to 1.56)	23/865	2.7	0.78	(0.44 to 1.41)
Admission for preterm labour	4/35	11.4	0.18	(0.04 to 0.7)	51/1974	2.6	0.67	(0.39 to 1.15)
PPROM	1/5	–	–	–	29/1283	2.3	0.57	(0.32 to 1.01)
Infection as indication for delivery	1/1	100	–	–	14/421	3.3	1.30	(0.64 to 2.64)
In utero transfer	95/295	38.2	1.44	(0.92 to 2.27)	34/1242	2.7	0.78	(0.45 to 1.36)
Unit policies of MgSO <sub>4</sub> use for pre-eclampsia								
Whenever possible	125/296	42.2	Ref.		–	–	–	–
Sometimes	106/339	31.3	0.73	(0.43 to 1.25)	–	–	–	–
Never	0/32	0.0	–	–	–	–	–	–
No response	29/53	45.3	0.70	(0.34 to 1.47)	–	–	–	–
for neuroprotection								
Whenever possible	–	–	–	–	47/260	18.1	Ref.	
Sometimes	–	–	–	–	24/749	3.2	0.08	(0.03 to 0.19)
Never	–	–	–	–	14/2173	0.6	0.02	(0.01 to 0.04)
No response	–	–	–	–	10/476	2.1	0.08	(0.03 to 0.24)

\*Defined as a diagnosis of eclampsia or HELLP, regardless of mode of delivery, or a diagnosis of pre-eclampsia and a prelabour caesarean section before 32 weeks of gestation. HELLP, Haemolysis, elevated liver enzymes, low platelet count; IUGR, intrauterine growth restriction; PPRM, preterm prelabour rupture of membranes. MgSO<sub>4</sub>, magnesium sulfate.

in these countries. To the best of our knowledge, however, there have been no new guidelines in other regions and no new evidence from randomised trials of the effectiveness of  $\text{MgSO}_4$  has been published.

## CONCLUSION

Evidence-based use of  $\text{MgSO}_4$  is applied less than expected in European obstetric units. Future research should focus on how to promote evidence-based use of  $\text{MgSO}_4$  for severe pre-eclampsia. Options include an increased focus on the existing guidelines, instituting audits and simulation training in the maternity ward to familiarise medical staff with the handling of  $\text{MgSO}_4$ . Our results showing low use of  $\text{MgSO}_4$  in non-pre-eclamptic women suggest that obstetricians are not convinced by available evidence on  $\text{MgSO}_4$ 's neuro-protective effect. Our results provide a useful baseline for evaluating practice changes as more evidence becomes available and more national societies develop guidelines for use of  $\text{MgSO}_4$  for neuroprotection.

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